REMARKS

Claims 1-21, 31-48 and 53 are pending. Claims 1-21, 31-48, and 53 stand rejected. Applicants wish to thank the Examiner for the courtesy of an interview on August 30, 2005. In this response, Applicants have presently amended claims 1, 3, 5, 31, 32, 34-37, 39-43, and 53. Applicants also submit herewith a Declaration of H. Greg Thomas under 37 C.F.R. § 1.132. In view of these amendments, the declaration, and as discussed below, it is submitted that the application is now in condition for allowance.

Summary of the Invention of the Present Application

The invention of the present application provides a composition including the tannate salts of active pharmaceutical ingredients, such as phenylephrine and pyrilamine. This composition is prepared by a method that enhances the uniformity of the amounts of the active pharmaceutical ingredients in the composition over that found in the prior art. The method of preparing the composition involves a conversion process, including mixing a dispersing agent and tannic acid in a suitable solvent to generate a mixture, referred to as a dispersion. A solution of the active pharmaceutical ingredients, as common salts or in the free base form, is added slowly to the dispersion to generate tannate salts of the active pharmaceutical ingredients. The tannate salts are directly processed into suitable dosage forms, such as a suspension or tablets. The use of the dispersion prevents the clumping and aggregation of the tannate salt

formed. Thus, as the tannate salts are further processed into dosage forms, the dispersion promotes uniformity of the amount of active pharmaceutical ingredients. Thus, each dosage unit of the dosage form (e.g., each tablet or each 5 ml of suspension) will include an amount of the tannate salts that is generally uniform to each other dosage unit (e.g., each other tablet or 5 ml of suspension). Further, the use of free base or common salt forms of phenylephrine and pyrilamine that are processed directly into tannate salts in the composition in situ, further aids in reducing variability of active pharmaceutical ingredients in final product. This is because there is less variability in the free base or common salts than in the tannate salts. Thus, by starting with a commonly available salt or free base of the active pharmaceutical ingredient, which is subsequently converted and incorporated in-situ as a tannate salt complex, the invention provides an efficient and reproducible method to manufacture liquid or semi-solid products containing tannate salt complexes as active ingredients.

As a result of the method used to prepare the compositions, the problem described in the application of prior art pharmaceutical compositions that contain variable, and sometimes sub-therapeutic, levels of active pharmaceutical ingredients is ameliorated by providing a composition including a generally uniform amount of active pharmaceutical ingredients from dosage unit to dosage unit. Since the tannate salts of phenylephrine and/or pyrilamine are generated and incorporated in-situ into the dosage

form during the manufacturing process, the purification and drying steps, which are generally required for the isolation of the tannate salts, are also eliminated.

New Matter Objections/Claim Rejections under 35 U.S.C. § 112

The Examiner has objected to the amendment, submitted with the Request for Continued Examination of July 22, 2004, under 35 U.S.C. § 132 as introducing new matter into the disclosure. In particular, the Examiner states that the phrase "being present in a plurality of dosage forms" is not supported by the disclosure. Following the amendment dated July 22, 2004, this phrase appeared in independent claims 1, 31, and 53 (each of the pending independent claims). Further, the Examiner also rejected these claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, due to the addition of the phrase "being present in a plurality of dosage forms."

In making the objection under § 132 and the rejection under § 112, the Examiner states that the application only discloses preparation of the composition as a single dosage form (either as a suspension or a tablet), but does not disclose the composition simultaneously as two different forms (i.e., suspension and tablet). By the amendment dated July 22, 2004, Applicants did not mean to suggest that both tablets and suspensions are formed in the same composition. Rather, Applicants meant that each of the plurality of tablets includes generally same amounts of the active pharmaceutical ingredient(s) as each of the other tablets (or alternatively that each

dosage of suspension contains generally the same amount of the active pharmaceutical ingredient(s) as each of the other dosages of suspension). Regardless, Applicants have removed the phrase "being present in a plurality of dosage forms" from claims 1, 31, and 53. In view of this amendment, Applicants respectfully request a withdrawal of the objection under § 132 and of the rejection under § 112.

Further, the Examiner has rejected claim 1 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that the phrase "being generally uniform in each of said dosage forms" is not clear, and the specification does not define how to ascertain the requisite degree of concentration or amounts of the active ingredients. Furthermore, the Examiner states that it is not clear what is being compared with. In response, Applicants have removed the phrase "being present in a plurality of dosage forms" from claims 1, 31, and 53. In view of the present amendments, Applicants respectfully request a withdrawal of the objection under § 112, second paragraph.

Claim Rejections 35 U.S.C. § 103

Claims 1-21, 31-48 and 53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,287,597 ("Gordziel") in view of U.S. Patent No. 5,599,846 ("Chopdekar"). Applicants respectfully disagree with the rejections. As will be discussed in greater detail below, Applicants submit that neither of these

references, alone or in combination, disclose or suggest a composition produced by method of an in-situ conversion to the tannate salt of the active ingredients to provide a dosage form which enhances uniformity of amounts of the active ingredients, as is provided by the claimed composition, due to the method recited in the composition claims.

Applicants first submit that independent claims 1, 31, and 53 include at least two recitations that render the amounts of active pharmaceutical ingredients more uniform in the claimed composition, thereby distinguishing the claimed composition from the compositions disclosed in the cited art. First, the recited use of a separate dispersion (including a dispersing agent such as magnesium aluminum silicate, xanthan gum, and cellulose compounds) prevents the aggregation of the tannate salts as they precipitate out of solution, thereby enhancing uniformity of amount of active ingredient from dosage unit to dosage unit. Second, the conversion process begins with the free base or common salt form of the active ingredient. Such forms exhibit less variability in amounts of active pharmaceutical ingredients, as opposed to the tannate form isolated and then used in the cited references. Thus, by starting with a form having less variability in amounts of the active, the claimed composition prepared in that manner also demonstrates greater uniformity of amounts of active ingredients over the cited references, once processed in situ into the tannate salt forms. These recitations of the claims will be discussed in greater detail below.

Claims 1, 31, and 53 each recite that the process for preparing the composition involves combining a solution (which includes active pharmaceutical ingredients) to a dispersion (including a dispersing agent and tannic acid). As described above, and throughout the application, the novel process of using a dispersion aids in increasing the general uniformity of the amounts of active pharmaceutical ingredients from batch to batch (and thus dosage unit to dosage unit) of the presently claimed composition, as opposed to the more variable levels of active pharmaceutical ingredients present in compositions of the cited art. Support for this may be found at least at page 4, lines 14-15, and page 11, lines 18-20 of the present application. The application at pages 4 and 11 describes that the presence of the dispersing agent and its use in a separate dispersion (which is not found in the cited art) prevents the clumping and aggregation of the tannate salt formed. Thus, as is described at least at page 11, lines 18-20, this method, by preventing clumping and aggregation of the tannate salt, promotes uniformity of the active pharmaceutical ingredients in the compositions formed.

Further, as recited in independent claims 1, 31, and 53, the active pharmaceutical ingredient is added in its free base or salt form. This further reduces variability and promotes uniformity of API in final product. At least, at page 3, line 14 through page 4 line 2, the application describes that one problem with present compositions is that the presence of low active percentages of antihistamine or

decongestant and the variable purity of commercially available antihistamine and decongestant tannate salts results in the stoichiometry of active free-based tannic acid in the tannate salts being different from batch to batch of compositions prepared. This results in significant dosing and processing problems during manufacturing, and results in commercially available pharmaceutical compositions that contain variables, and in some instances, subtherapeutic levels of active pharmaceutical ingredients. However, by using the free base or common salt form, as in the method of the present composition claims, the present invention reduces this variability. This, however, is not seen in the cited art.

For example, both Chopdekar and Gordziel describe processes for the preparation of tannate forms of pyrilamine and/or phenylephrine, which then may be used to prepare compositions including those tannate salt forms of phenylephrine and pyrilamine. Applicants submit that the use of those pyrilamine tannate and phenylephrine tannate forms, as in Chopdekar and Gordziel results in compositions that exhibit greater variability of active ingredients in each batch or dosage unit of the final drug composition product as compared to the presently claimed composition prepared by the method recited in those claims. (See Declaration of H. Greg Thomas, paragraph 5.)

Applicants submit that this becomes clear when comparing the specifications of active ingredient raw materials used during the manufacture of tannate

pharmaceutical compositions, such as those described in Chopdekar and Gordziel, versus that of the presently claimed composition, which use the method recited in claims 1, 31, and 53. In particular, the content variation for the common salt of pyrilamine is 2.50%, whereas the content variation range for the tannate salt of pyrilamine is 6%. And the content variation range for the common salt of phenylephrine is 5%, whereas the content variation range for the tannate salt of phenylephrine is 9%. In each case, there is more variation in the active ingredient added to the formulation as tannate salt and processed into finished pharmaceutical compositions, such as those set forth in Chopdekar and Gordziel. The decrease in active ingredient variability inherent in the claimed compositions due to the use of the method recited in the claims would be 3.50% for pyrilamine and 4% for phenylephrine. In the manufacture of pharmaceutical products, Applicants submit that these are very significant reductions in content variability. (See Declaration of H. Greg Thomas, paragraphs 9 and 10.)

Thus, in order for the compositions of Chopdekar and Gordziel to achieve the same level of active ingredient content uniformity as would be exhibited by the presently claimed composition, a correction in the amount added to the formulation must be made each time a batch is prepared using a different lot of tannate salt raw material. In fact, such a correction must be performed if the finished composition is to meet current international pharmaceutical product standards of 95%-105% of the target active ingredient amount. Failure to do so may result in a subpotent and unmarketable

product. The necessity of performing such a calculation decreases the efficiency of the manufacturing process and introduces another possible source of error. (See Declaration of H. Greg Thomas, paragraph 11.)

The general cause of increased content variability that is inherently produced using the prior art methods of Gordziel and Chopdekar is not difficult to explain. Each step or operation performed in a manufacturing environment introduces some level of variability into the finished product. When the operation in question, such as a method of Gordziel and/or Chopdekar, involves isolating a tannate salt, such as by beginning with the free-base form and then converting to the tannate salt, and thereafter processing those tannate salts into a composition, the variability is focused on the amount of active ingredient contained in the finished pharmaceutical product. By eliminating the additional isolation step required by the prior art that is a potential source of increased content variability, the compositions presently claimed by the Kiel process are able to provide a consistently better finished product. (See Declaration of H. Greg Thomas, paragraph 12.)

The decreased content variability that results in the claimed compositions due to the recited method has many real world advantages. A better finished in the pharmaceutical industry means a safer drug. The principal properties affected by converting a drug to the tannate salt form is solubility, which normally decreases after conversion to a tannate from a hydrochloride salt or bromide salt. The decreased

solubility attained in this matter gives the drug prolonged action characteristics. Changes in the content of the tannate salt in a final drug product can potentially alter the overall amount of drug taken, as well as the rate at which the drug enters the body. Understandably, then, increased variability in drug content leads to increased risk to the patient taking the drug product. The need for increased safety and content uniformity is multiplied by the fact that many of the tannate drug products are designed for use by children. (See Declaration of H. Greg Thomas, paragraph 13.)

Applicants submit that since this general uniformity is generated by the particular process of the claimed invention, the differing steps of the present process over that of the prior art provide for differences in the compositions that are formed by the respective processes: namely, that each dosage unit formed includes amounts of active pharmaceutical ingredients that are generally uniform when compared to all other dosage units formed. Applicants further assert that since neither Gordziel nor Chopdekar disclose the process steps necessary to generate such general uniformity of active pharmaceutical ingredients, the compositions produced in Gordziel and Chopdekar do not exhibit such general uniformity. Thus, in the present invention, the method changes the product over that found in the cited art. As a result, Applicants submit that, based on the method, the claimed product is patentable over the cited art.

Applicants note that neither Chopdekar nor Gordziel discloses the process by which the general uniformity of active pharmaceutical ingredient in the present

composition is achieved. In fact, as previously noted, both Chopdekar and Gordziel describe the "old" routes of preparation, which Applicant describes in the application as forming compositions which vary in the amount of active pharmaceutical ingredient from dosage unit to dosage unit. Thus, Applicant submits that the composition disclosed in Gordziel or Chopdekar will not exhibit such general uniformity, and rather disclose compositions which exhibit variable levels of active pharmaceutical ingredient from dosage unit to dosage unit of the composition. As a result, Applicants submit that it cannot be the case that the composition disclosed in Gordziel is the same as the composition claimed in the present application. Applicants further submit that a combination of Gordziel with Chopdekar also cannot render such a composition obvious, since Chopdekar also does not describe the process used to achieve the general uniformity of the amounts of active pharmaceutical ingredients, and thus does not disclose a composition exhibiting such general uniformity. Thus, Applicants assert that any combination of Gordziel and Chopdekar fails to teach every element of the invention as presently claimed.

In view of the above, Applicants assert that the combination of the Gordziel and Chopdekar references do not teach all the limitations of independent claims 1, 31, and 53 as presently amended, and further assert that the process of the independent claims renders a different product than that of Gordziel and Chopdekar.

As such, Applicants respectfully request a withdrawal of the rejection of claims 1-21, 31-48, and 53 under 35 U.S.C. § 103.

Claim Rejections Double Patenting

Claims 1-21, 31-48, and 53 have been provisionally rejected under the judicially created doctrine of double patenting over claims 1-21, 31-48, and 53 of co-pending application 10/645,977. In view of the claims as presently amended, Applicants respectfully disagree.

Applicant first notes that each independent claim 1, 31, and 53 have been presently amended to recite active pharmaceutical ingredients "consisting essentially of" phenylephrine and pyrilamine. Thus, Applicants respectfully disagree with the Examiner's statement that the interpretation of the present claims allows for the inclusion of any other unspecified components by reciting "comprising." Thus, Applicants submit that the inclusion of dextromethorphan in the claims of co-pending application 10/645,977 does not render the present claim as obvious. Applicants therefore respectfully request a withdrawal of the rejection of claims 1-21, 31-48 and 53 under the judicially created doctrine of double patenting.

Conclusion

For the foregoing reasons, it is submitted that all claims are patentable and a Notice of Allowance is respectfully requested.

Applicants authorize the Commissioner to charge Deposit Account No. 23-3000 in the amount of $510.00 for a three-month extension for a small entity under 37 C.F.R. 1.17(a)(3). Applicants believe that no further fee is due with this submission. If, however, any additional fee or surcharges are deemed due, please charge same or credit any overpayment to Deposit Account No. 23-3000.

The Examiner is invited to contact the undersigned attorney with any questions or remaining issues.

Respectfully submitted,
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